construct did so more stably, but soluble TNFa could still be found at significant levels in the cell supernatants (see, e.g., Figure 2B, lane 5, at Mueller, *et al.*, page 38114, and Specification at paragraph 007). Applicants have therefore submitted that Mueller, *et al.* suggests only that removal of the disclosed portion of Domain III of the TNFa molecule will reduce release of soluble TNFa in certain cell types.

Kipps, et al. suggests a wide variety of TNF family chimera, including ones containing one or more domains from the CD154 molecule. Construction of the disclosed CD154 chimera can produce molecules that are expressible on the surface of cells from which they would not otherwise be expressed; e.g., a chimera including certain murine CD154 elements may be expressible on the surface of human CD40+ cells (*see, e.g.,* Kipps, *et al.* at US Pat. No. 7,070,771, Col. 22, lines 33-37, and Claim 1 thereof).

Applicants submit that the claimed molecules represent a particular combination of elements (a CD154 Domain III element lacking a cleavage site with a TNFa Domain IV element that binds a cognate receptor) that one would not readily select from the range of variables suggested by the cited art. Moreover, even if one was to happen upon the particular selection claimed, the result—near elimination, not just reduction, of soluble TNFa release—could not have been predicted.

According to *KSR Int'l Co. v. Teleflex, Inc.*, 550 US __, 2007 WL 123837, at 12 (2007), "[t]he combination of familiar elements according to known methods is likely to be obvious *when it does no more than yield predictable results.*" (Emphasis added). Here, Applicants submit that one could construct a wide range of different constructs following Kipps, et al. (to obtain expression in expression-incompetent cell types), and might try to modify cleavage sites in the chimera (to enhance stability). If one did so, one might possibly hope that release of soluble TNFa could be reduced from molecules lacking a cleavage site from Domain III of the TNFa molecule and/or that the chimera might be expressible in otherwise expression-incompetent cell

types. The invention, however, yields much more--a CD154 (Domain III)-TNFa (Domain IV) chimera lacking a cleavage site in Domain III of the CD154 element from which soluble TNFa release from transfected cells is virtually eliminated.

As discussed during the interview, the cited references would not readily lead one of ordinary skill in the art to predict that soluble TNFa release could be eliminated from cells transfected with the claimed chimera in particular. In corroboration of that conclusion, enclosed is the Declaration of Dr. Kenneth A. Foon, now a Professor of Medicine at the University of Pittsburgh. After detailed consideration of the cited references, Dr. Foon concludes:

> Nothing in the references points one to select a CD154/TNFα chimera lacking a metalloproteinase site in particular, nor do the references offer a reasonable basis upon which to expect that cleavage from such a chimera would be abrogated to the same or greater degree than demonstrated by Mueller, et al. for the TNF molecule they tested. Even in view of the Kipps application's disclosure, one could not have predicted, *a priori*, the best combination of TNF family member segments to fuse to the domain IV of TNF to create a stabilized molecule.
>
> Foon Declaration, paragraph 7.

Based on all of the foregoing, as well as the Declaration of Dr. Prussak submitted with the Amendment of October 5, 2006, Applicants respectfully submit that the invention of the pending claims is not obvious over Kipps, *et al.*, in view of Mueller, *et al.* Reconsideration and withdrawal of the claims rejection under 35 USC §103 is therefore requested.

Applicants believe that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Check number 585770 in the amount of $620.00 is enclosed as payment for the Request for Continued Examination fee ($395.00) and the Petition for two-month Extension of Time fee ($225.00). No other fee is believed due in connection with this Amendment. If any additional fees are due, the Commissioner is hereby authorized to charge any fees that may be required by this paper to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is attached.

Respectfully submitted,

Date: May 17, 2007

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